REMARKS

Claims 5-8, 13-28 and 33 were pending in the application. These claims have been canceled. New claims 34 to 53 were added. Support for new claims can be found throughout the specification and the originally filed claims, for example, Example 2 at pages 26-30; page 12, lines 4-12; page 12, line 29 to page 13, line 18; page 8, lines 1-7; page 10, lines 21-30; and page 21, lines 11-15. No new matter was added.

Reconsideration of the present application is respectfully requested.

Rejections under 35 U.S.C. § 112, 1st Paragraph

The Examiner rejected claims 5-8, 13-18, and 33 under 35 USC § 112, first paragraph for lack of written description and enablement. *Inter alia,* the Examiner appears to doubt the connection between TGF-β levels and disease. Applicants believe that there is sufficient scientific evidence to support such a connection, some of which evidence is discussed in the specification. However, in the interest of expediting prosecution, Applicants have canceled claims 5-8, 13-18, and 33 and the rejections are now moot.

New claims

Applicants believe that new claims 34-53 address prior Examiner's concerns. Early and favorable consideration of the new claims is respectfully requested.

New claims 34-53 were added based on Applicants' findings described in Example 2 at pages 26-30 of the specification. Applicants wish to emphasize the following important aspects of their findings.

(1) The level of TGF-β in a blood sample of a human (or a veterinary animal) differs from one subject to another, *i.e.,* inter-individual variability is high (*see e.g.* absolute values of TGF-β in pg/ml, specification, page 28, 2nd par. under "Results").

(2) When blood samples from different individuals are incubated with a series of flavanols and procyanidins, the percent change of TGF-β levels relative to respective

control samples varies from positive to negative even for the same compound. This pattern was observed for each compound tested. This is best illustrated in Figure 1.

In Figure 1, each circle in the scatter plot corresponds to a single individual. Each individual was tested with each of the compounds, *i.e.*, flavanols (monomer) or procyanidins (dimer through decamer). Figure 1 illustrates the differential response of each of these individuals to each of the tested compounds. Because some of the individuals responded to the same test compound by decreasing their TGF-β level and others by increasing their TGF-β level (and this was observed for all tested compounds), Applicants analyzed the data searching for a correlation or a pattern or a trend that could explain this finding.

(3) Applicants discovered that this differential response was due to the differences in the starting (*i.e.*, baseline) levels of TGF-β, *i.e.*, the levels prior to exposure to the tested compounds. When the tested individuals were categorized on the basis of their starting TGF-β levels, a clear trend was observed in the way in which the tested compounds modulated TGF-β levels. This is best illustrated in Table 3 of the specification (page 30).

Thus, as shown in Table 3, tested individuals were divided into two groups, low baseline producers (their TGF-β levels were less than 6000 pg/ml, 3604 +/- 568 pg/ml, see specification, page 28, 2nd par. after "Results") and high baseline producers (their TGF-β levels were 7910 +/- 695 pg/ml, see specification, page 28, 2nd par. after "Results"). Referring to Table 3 (page 30), individuals categorized as low baseline producers responded to monomer with an increase in their TGF-β levels; in contrast, the same compound, when administered to high baseline producers, caused a decrease in TGF-β levels. The same pattern is observed for all other tested compounds (also shown in Table 3). In other words, it is the starting level of TGF-β which determines how an individual will respond to a given flavanol or procyanidin. Therefore, if a subject responds to monomer by increasing its TGF-β, it is classified as a low baseline producer; conversely, if a subject responds to monomer by decreasing its TGF-β, it is classified as a high baseline producer.

Based on the above findings, TGF-β screenings as recited in claim 34 *et al.* are performed. Such screenings are useful for the study of the underlying mechanisms of differential responses of individuals and TGF-β-modulating mechanisms of flavanols and procyanidins, and other purposes.

Conclusion

In view of the above amendment and remarks, Applicants believe that the application is in condition for allowance. Such action is respectfully requested.

Respectfully submitted,

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Nada Jain
Reg. No. 41,431

NADA JAIN, P.C.
560 White Plains Road
Tarrytown, NY 10591
Telephone: 914 333-0610